**REMARKS**

The restriction between process and product has been maintained, and in response, Applicants cancel the non-elected product claims without prejudice. Applicants thank the Examiner for reconsidering and withdrawing the species election requirement. Added claim 21 depends from claim 7 and is supported, e.g. by the language of claim 16. No new matter is added.

A substitute Declaration by the Inventors (executed separately by each of the two inventors on a different declaration form) accompanies this response.

In response to the objection to Figure 1, Applicants submit herewith a "Replacement Sheet" of Figure 1 in which the right panels are believed to be fully legible for purposes of understanding what is depicted. The legends to the graphs in the left panels of Figure 1 are in English. It is noted that black and white photographs showing, *inter alia*, cell cultures are normally acceptable in drawings. 37 C.F.R. 1.84(b)(1). This replacement sheet is believed to overcome the objection to drawing Figure 1.

The Specification has been amended as suggested on page 42.

The claims have been currently amended in response to each of the objections, and rejections under 35 USC 112, set out on pages 4-6 of the Official Action. The Examiner's detailed attention to the claim form is appreciated, and the suggestions made in the Official Action have been adopted. It is believed that all objections and rejections are overcome by this amendment.

**Prior Art Rejections**

In the Official Action, claims 1-3, 5-9 and 12-17 were rejected as anticipated by Hoerr, US Published Application 20060188490 (Hoerr), filed January 30, 2006, the reference date for applying Hoerr under 35 USC 102.

Claims 1-9, 12-15 and 17 were rejected as anticipated under 35 U.S.C. 102(e) by US Published Application 20050112141 (Terman) filed September 8, 2004 and identified as a continuation of an application filed August 30, 2000.

Claims 1-17 were rejected under 35 USC 103 as unpatentable over Terman in view of Draghia-Akli et al. or Weiner et al.

**The Claimed Subject Matter has an Effective Filing Date of September 2, 2004**

With this response, Applicants submit verified English translations of: i) German Application DE 10 2004 042 546.9, filed September 2, 2004 (**Exhibit A**); and ii) PCT/EP2005/09383, filed August 31, 2005 (**Exhibit B**)[1].

The subject matter of amended claim 1 (administering to a mammal of at least one mRNA encoding an antigen from a pathogen or encoding a tumour antigen, and separately administering an mRNA encoding a cytokine, to achieve immunostimulation in the mammal) is disclosed in the priority applications at the following passages:

Administration to a mammal: Page 5, lines 11-19 and page 18, ll. 28-29 of Exhibit A; Page 5, lines 12-22 of Exhibit B.

Cytokine mRNA: Page 18, lines 28-29 of Exhibit A (cytokine can be in the form of RNA); Page 5, line 20 of Exhibit B.

Separate administration of the mRNA and the cytokine: Page 7, line 30 – page 8, line 5 of Exhibit A; Page 8, line 29 – Page 9, line 15 of Exhibit B.

Immunostimulation: Page 9, line 28 – page 10, line 20 of Exhibit A; Page 11, line 26-page 12, line 20 of Exhibit B.

[1] The referenced page numbers of the sheets of Exhibit A are hand written in the lower right corner of each page.

Since Applicants' claim to priority to the filing date of September 2, 2004 is perfected by the filing of the relevant English translations, it is submitted that the Hoerr reference – which has a date for purposes of 35 USC 102(e) of January 30, 2006 and a publication date even later – is not applicable as prior art against the present application. Accordingly, it is urged that the rejection based on Hoerr be withdrawn.

**Terman Does not Disclose the Subject Matter of the Amended Claims**

Reconsideration of all rejections based in whole or in part upon the Terman publication is requested in view of the present amendment to the claims. As now claimed, the administration of the mRNA in step (a) is separate from the administration of the mRNA in step (b).

Terman concerns generally the activation of cells for use in adoptive immunotherapy. A number of embodiments which use a "superantigen" (SAg) in combination with another substance to generate activated cells are disclosed.

In one specific embodiment Terman uses both a nucleic acid encoding a SAg and a nucleic acid encoding a cytokine, wherein the nucleic acid encoding the SAg is fused in frame to the nucleic acid encoding a cytokine (e.g. RANTES, IL-5, IL-2; IL-12; IL-13; INF), i.e. to form one (bicistronic) nucleic acid encoding both proteins. Alternatively, the two nucleic acids of Terman are used to cotransfect cells, i.e. the two nucleic acids are administered simultaneously to the same site. See [0307] – [0309]. Cells transformed with such constructs are said to be useful for adoptive immunotherapy, as disclosed for example in Example 16.

Terman does not even specify the nature of the nucleic acid to be administered in this specific embodiment. Even though Terman discloses that nucleic acids may be DNA and RNA and many other nucleic acid (see [0056] – [0057]), Terman does not mention mRNA. Furthermore, Terman only refers to nucleic acids more generally in relevant sections [0307] – [0309] discussed above, i.e. DNA and RNA may be used equally. No preference is given.

However, as already intensively discussed in the introductory part of the present specification, the use of DNA risks the uncontrolled propagation of the gene-therapeutically

active genes introduced, and the viral genes introduced, due to possible recombination events. In addition, DNA vaccination has further potential safety risks. The recombinant DNA injected must first reach the cell nucleus, and this step can already reduce the efficiency of DNA vaccination. In the cell nucleus, there is the danger that the DNA integrates into the host genome. Integration of foreign DNA into the host genome can have an influence on expression of the host genes and possibly trigger expression of an oncogene or destruction/inactivation of a tumour suppressor gene. A gene – and therefore the gene product – which is essential to the host may likewise be inactivated by integration of the foreign DNA into the coding region of this gene. There is a particular danger if integration of the DNA takes place into a gene which is involved in regulation of cell growth, in which case the host cell may enter into a degenerated state and lead to cancer or tumor formation. A further disadvantage is that the DNA molecules remain in the cell nucleus for a long time, either as an episome or, as mentioned, integrated into the host genome. This leads to a production of the transgenic protein which is not limited or cannot be limited in time, and to the danger of an associated tolerance towards this transgenic protein. The development of anti-DNA antibodies and the induction of autoimmune diseases can furthermore be triggered by injection of DNA.

Such a teaching, however, is clearly missing in Terman. Even in the case that Terman may use RNA for the purpose of administering an antigen and a cytokine in general, Terman does not indicate or even suggest the use of mRNA as claimed.

Additionally, Terman does not overcome the disadvantage generally known for RNA or mRNA vaccines in the art. Most important, as discussed in the specification, page 4, last paragraph, a great disadvantage of the mRNA vaccines generally known in the prior art is that only a humoral immune response (Th2 type) is triggered by an mRNA vaccination. However, all viruses and numerous bacteria, such as, for example, mycobacteria and parasites, penetrate into the cells, multiply/proliferate there and are thus protected from antibodies. In order to cause an antitumoral or antiviral immune response in particular, it is necessary to trigger a cellular immune response (Th1 type). Such a cellular immune response, however, cannot be triggered

with the simultaneous administration embodiments disclosed in Terman ("cotransfection" or "bicistronic nucleic acid").

This disadvantage is clearly rendered moot by separately administering to a mammal in need of immunostimulation both an mRNA encoding an antigen from a pathogen or tumour and an mRNA encoding a cytokine, in accordance with the present invention as now claimed.

As explained in the current specification, e.g. at page 9, immunostimulation in a mammal is particularly effective when the mRNA and the cytokine mRNA are separately administered and in particular when the cytokine mRNA of step (b) is administered after the mRNA of step (a). Such an administration mode provides a significantly intensified immune response, wherein not only a humoral immune response (Th2 type) is triggered but also a shift from a Th2 type response to a Th1 type response. Such an effect could not have been predicted from the disclosure of Terman.

For these reasons, the subject matter as now claimed is not anticipated by Terman and would not have been obvious from Terman either alone or further in view of additional prior art disclosing modifications to mRNA.

**Other Matters**

A supplemental information disclosure statement is being filed together with this response.

It is noted for the record that certain claims of the current application (in the form they existed prior to the present amendment) were cited in co-pending application Ser. No. 11/025,858 to reject certain claims pending therein for obviousness-type double patenting.

The references cited in the accompanying information disclosure on form SB/08 have been collected from commonly-assigned pending applications which claim potentially-related subject matter, namely: Ser. No. 11/342,392; Ser. No. 11/632,802; Ser. No. 10/729,830; Ser. No.

11/025,858; Ser. No. 10/870,110; Ser. No. 11/748,181; Ser. No. 12/446,912; and Ser. No. 12/502,637.

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In view of the above, consideration and allowance of claims 1-17 are respectfully solicited.

The Office is authorized to charge any necessary fees to Deposit Account No. 03-2775.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 03-2775, under Order No. 22122-00006-US1 from which the undersigned is authorized to draw.

Dated: February 9, 2010

Respectfully submitted,

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Attachments:
1. Substitute Declaration, signed by Inventors
2. Substitute Figure 1
3. Exhibit A – verified translation of DE 10 2004 042 546.9
4. Exhibit B -- verified translation of PCT/EP2005/09383